REMARKS

Upon entry of the foregoing amendment, claims 1-46 are pending in this application. Claims 14-44 have been withdrawn from consideration as being directed to a non-elected invention. Claims 1-13 have been amended. Applicants reserve the right to pursue any deleted subject matter in a continuing or divisional application.

Support for the amendments to claims 1-13 for the phrase "non-human vertebrate" is found, *inter alia*, on page 12, lines 21-22; page 28, lines 1-4; and, elsewhere throughout the specification. Further, claims 1-13 were amended along lines suggested by the Examiner ("non-human animal;" *See*, Office Action, page 10, last sentence, "Claim Rejections-35 U.S.C. § 101").

Support for the amendments to claims 1 and 2 for the term "bone" in the phrase "bone cells" is found, *inter alia*, on page 10, lines 19-21 ("bone tissue"); and, elsewhere throughout the specification.

Claim 4 has been amended to now claim SEQ ID NO: 2, the nucleotide sequence encoding the HBM protein. The amendment to claim 4 is in keeping with the Office Action restatement of the restriction requirement (page 5, second full paragraph, and page 8, first full paragraph), describing claims 1-13 as being directed to a transgenic animal and, *inter alia*, SEQ ID NO: 2. Support for the amendment to claim 4 is found, for example, on pages (page 31, lines 8-16; page 34, lines 14-24); and, elsewhere throughout the specification. Claim 13 has likewise been amended to claim the HBM gene in order to maintain correct antecedent basis with claim 4. Support for the amendments to claim 13 is found, for example, on page 145, line 24 through page 149, line 29; and, elsewhere throughout the specification.

Support for new claim 45, is found, *inter alia,* on page 12, lines 23-26; page 148, lines 14-16; and, elsewhere throughout the specification.

Support for new claim 46 is found, *inter alia,* on page 12, lines 26-27, and, elsewhere throughout the specification.

No new matter is believed to be added by the amendment and entry is respectfully requested.

A. RESTRICTION REQUIREMENT

Applicants acknowledge with thanks the withdrawal of the restriction requirement comprising 78 groupings to a new restriction into 10 groups. At pages 2-8, the Office made the restriction requirement final, setting forth new groupings of inventions as follows:

I. (claims 1-13) "A transgenic animal having somatic and/or germ cells comprising a nucleic acid which comprises a promoter region capable of directing protein expression in an animal and/or human cells that is operably linked to a sequence comprising at least 15 contiguous nucleotides of SEQ ID NO. 2 including at least the thymine at position 582 of SEQ ID NO. 2." Office Action, page 5.

II. (claims 14-18, 42-44) "A transgenic animal having a genome comprising an alteration of the gene encoding LRP5 wherein the alteration is caused by the introduction of a nucleic acid for gene targeting by homologous recombination into embryonic stem cells or pluripotent cells comprising a first section homologous to mouse LRP5 gene and a second section homologous to another section of mouse LRP5 gene and between the first and second section a middle section comprising an engineered deletion of a portion of the LRP5 gene, a nucleic acid is capable of homologous recombination with the endogenous gene." Id. at 5.

III. (claims 19-20) "A transgenic animal having a genome comprising an alteration of the gene encoding LRP6 wherein the alteration is caused by the introduction of a nucleic acid for gene treating by homologous recombination into embryonic stem cells or pluripotent cells comprising a first section homologous to mouse LRP6 gene and a second section homologous to another section of mouse LRP6 gene and between the first and second section a middle section comprising an engineered deletion of a portion of the LRP6 gene, a nucleic acid sequence change, or a nucleic acid insertion, and wherein the nucleic acid is capable of homologous recombination with the endogenous gene, wherein the transgenic animal has modulated Wnt activity, DKK activity, lipid levels or bone mass." Id. at 5-6.

IV-VIII. (claims 21-29 and 32-37) "A method for studying bone mass development, a method for identifying surrogate markers of bone formation/resorption, a method for studying the effects of a test compound and the HBM gene on cardiac disorders, a method of screening of screening of cardio-protective treatments for bone mass modulation effects, or a method for identifying genes associated with bone mass, comprising the steps of:

a) providing a first group of animals

b) measuring at least one parameter of bone development in the animals wherein the group of animals are selected from among:

IV. animals comprising a transgene for expressing LRP5

V. animals comprising a transgene for expressing LRP6

VI. animals in which the native LRP6 knocked out and HBM or another variant has been knocked into the LRP6 gene of the animals' genome,

VII. animals in which the native LRP5 is knocked out,

VIII. animals in which the native LRP6 is knocked out."

The method further comprises a step of administering a chemical compound and/or a surgical procedure to at least some of the animals prior to measuring at least one parameter of bone development in the animals." Office Action, page 6-7.

IX. (claims 30, 31) "A method for studying an effect of HBM on bone disorders comprising the steps of:

a) providing embryos of animals with a bone disorder phenotype,

b) introducing the nucleic acid of claim 1 and claim 4 into a first group of the embryos,

c) transferring the embryos to pseudopregnant mice;

d) measuring at least one paragmeter of development in the resulting mice." Id., at 7.

X. (claims 38-41) "A nucleic acid for gene targeting by homologous recombination comprising a first section homologous to mouse LRP5 gene and second section homologous to another section of mouse LRP5 gene, and between the first and second section, a middle section comprising an engineered deletion of a portion of the LRP5 gene, a nucleic acid sequence change, or a nucleic acid insertion, and wherein the nucleic acid is capable of homologous recombination with the endogenous gene." Office Action, page 7.

Applicants acknowledge the finality of the restriction requirement. As the Office is aware, if the elected claims are directed to a product and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claims will be rejoined. (M.P.E.P. § 821.04, "Rejoinder," Volume 1, eighth edition, Revision 2, May 2004). Upon allowance of one or more of claims 1-13, Applicants will seek rejoinder of pertinent method claims.

B. INFORMATION DISCLOSURE STATEMENT

The Office asserts the information disclosure statement filed January 16, 2004 fails to comply with 37 CFR § 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The Office noted the IDS has been placed in the application file, but the information referred to therein has not been considered.

In reply thereto, provided herewith is a copy of each of the Courseaux *et al.* and Schneider *et al.* references. Attached for the convenience of the Examiner is a clean copy of the PTO-1449 form previously submitted. Applicants respectfully request consideration of each document and return of an executed PTO-1449 form indicating such consideration with the next communication from the Office.

C. REJECTIONS

1. Obviousness-type Double Patenting

The Office provisionally rejected claims 1-5 and 7-13 under 35 U.S.C. § 101 as claiming the same invention as that of claims 1-4, 6-8, 10 and 12-15 of copending application No. 10/477,238 ('the 238 application'). The Office alleges that claims 1-5 and 7-13 of the instant application ('287) are the same as claims 1-4, 6-8, 10 and 12-15 of the '238 application. Claim 5 is provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claim 5 of the copending '238 application. Although the conflicting claims are not identical, they allegedly are not patentably distinct from each other because claim 5 of the instant application ('287), drawn to a transgenic animal of claim 1, wherein the promoter region is a bone specific promoter region, encompasses claim 5 of '238, drawn to a transgenic animal of claim 1 wherein the promoter region is osteocalcin, osteopontin, and bone sialoprotein. The rejection is respectfully traversed.

Applicants request the rejection be held in abeyance until such time as one or more claims are declared allowable in either this or the '238 application. At that time, Applicants will determine whether the filing of a Terminal Disclaimer is appropriate.

2. Rejections under 35 U.S.C. § 101

Claims 1-3, 5 and 7-12 are rejected under 35 U.S.C. § 101 because the claimed invention is allegedly directed to a nonstatutory subject matter. The Office alleges claims 1-3, 5 and 7-12 encompass transgenic humans, which is nonstatutory subject matter. The rejection is respectfully traversed.

In reply, and without acquiescing to the propriety of the rejection, claims 1-13 have been amended to include the phrase "non-human." The amendments to claims 1-13 are believed to moot the rejection. Reconsideration and withdrawal of the rejection is respectfully requested.

3. Rejections under 35 U.S.C. § 112, first paragraph (enablement)

Claims 1-13 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Office alleges the claims contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The rejection is respectfully traversed.

The Office arguments, spanning Office Action pages 10-23, are summarized and discussed below.

a) The Office argues the claimed invention broadly encompasses any transgenic animal, but the specification at the time of filing teaches transgenic mice comprising a transgene construct comprising a nucleic acid sequence encoding HBM operably linked to a CMV β-actin promoter (specification, page 170, lines 20-21), transgenic mice comprising a transgene construct comprising a nucleic acid sequence encoding HBM operably linked to a type 1 collagen promoter (specification, page 170, lines 1-2), and transgenic mice comprising a nucleic acid sequence encoding LRP 5 operably linked to a type 1 collagen promoter (specification, page 179, lines 1-3). The Office further argues the specification as filed does not teach an artisan how to overcome the unpredictability associated with the insertion of a transgene into the genome of an animal. The Office arguments focus on two main points as the basis for the alleged unpredictability:

1) the randomness in which the transgene integrates into the host's genome, citing the teachings of Cameron (Cameron (1997), *Molecular Biotechnology*, 7: 253-265; arguing a feature common to many transgenic experiments is the unpredictability transgenic lines produced with the same construct frequently displaying different levels of expression) and,

2) the expression levels which do not correlate with the number of transgene copies integrated. The Office argues:

> "Such copy number-independent expression patterns emphasize the influence of surrounding chromatin on the transgene. .... Thus, an artisan cannot predict where a transgene will integrate in the host genome, how many copies of a transgene will integrate into the host genome, what the transgene expression pattern is, of the resulting transgenic animal (with regards to how much transcript is produced by the cell and with regards to in which tissues express transgene, as enhancers from the host's genome may also influence transgene expression), and what the subsequent phenotype(s) is of the transgenic animal. .... With regards to the instant invention, the phenotype observed in the transgenic mice is an increase in bone mass. The detectable increase in bone mass is dependent on the amount of transgene produced. In light of the teachings of Cameron and Mench, any transgenic animal comprising a transgene comprising SEQ ID NO. 1 of SEQ ID NO. 2, is not enabled for its full breadth of encompassing any transgenic animal comprising a transgene comprising SEQ ID NO. 1 or SEQ ID NO. 2 operably linked to a bone specific promoter or a ubiquitous promoter, as an artisan would need to characterize each transgenic animal made and determine if whether enough copies of transgene had integrated into the genome, and if enough transgene is being expressed (as some transgene may insert near a repressor) such that a phenotype could be detectable. As such, in order for an artisan to predict all the possible phenotypes that result from making transgenic animals is undue experimentation."
>
> Office Action, at pages 13-14.

However, the Office has over-broadly formulated the rejection. Contrary to the Office's interpretation, independent claims 1and 2 (now newly amended) do not claim a transgenic animal overexpressing the transgene (emphasis added). Claims 1-3 do not claim any particular copy number which must be inserted, any particular site of insertion into the genome, or any particular tissue pattern of expression. Claims 1-3 do not require transgene expression, let alone any particular level of protein expression. Claims 1-3, as a whole, are directed, *inter alia,* to transgenic non-human vertebrate animals comprising a transgene and a promoter operably linked thereto. Thus, the impact of randomness and copy number of integrated transgenes on level of expression is irrelevant to the invention claimed in claims 1-3. Further, the specification defines a transgenic animal on page 28, lines 5-11, and discloses, *inter alia*, the introduced DNA molecule may be integrated within a chromosome or it may be **extra-chromosomally replicating DNA**, thus making irrelevant any Office arguments based on "site of integration."

In any case, one of skill would easily be able to determine whether or not any particular transgenic animal is carrying the transgene and/or expressing the transgene simply by using the techniques for monitoring gene presence as disclosed in the specification. *See*, for example, specification page 37, lines 1-7, disclosing such methods as physical mapping by screening of libraries; page 40, lines 9-27, disclosing identification of gene by computational methods and direct cDNA selection; page 41, lines 10-22, disclosing the Northern blot technique; and elsewhere throughout the specification for techniques well known and available to one of skill in the art at the time the application was filed. Therefore, a rejection alleging unpatentability based on copy number and site of insertion, for example, is erroneous.

The arguments above concerning claims 1-3 are pertinent to claims 4-13 and are incorporated herein. Claim 4 is directed, *inter alia*, to a non-human vertebrate transgenic animal (hereafter referred to simply as "transgenic animal" for ease of reading), wherein the bone mass is modulated relative to nontransgenic animal of the same species in more than one parameter. Claim 4 has been amended to recite "SEQ ID NO: 2" which is the nucleotide sequence of HBM (Figures 6A-6J). The protein encoded by the HBM gene (i.e., SEQ ID NO: 4) has the property of causing elevated bone mass while the protein encoded by the LRP5 gene does not (specification page 31, lines 20-22). The specification provides guidance and methods enabling one of skill to characterize each transgenic animal to determine if the claimed characteristics (parameters) were in fact present and modulated. *See*, for example, page 33, lines 15-28, disclosing methods of assessing bone modulation by measuring parameters such as bone mineral density and bone mineral content (measured by pDXA X-ray methods); bone size, bone thickness or volume (measured by X-ray); bone formation rates (measured by, for example, calcium labeling); and, total, trabecular and mid-shaft density (measured by pQCT and μCT methods).

Since no single or specific combination of parameters or level of effect is claimed, one does not have to determine the copy number of integrated transgenes (or the site of integration for that matter) to determine if "enough transgene is being expressed such that a phenotype could be detected." One of skill is not required to "predict" all the possible phenotypes that result; one only has to use the methods and guidance disclosed (as discussed above) in the specification to monitor phenotype expression. Moreover, even if each transgenic animal comprises one or more copies of the transgene but exhibits no change in phenotype, the Office is reminded that some inoperative embodiments are allowed. The Office is reminded that Applicants are not claiming "insertion of a transgene into the genome of an animal" (Office Action, page 14, last sentence), because, for example, the gene may be carried extrachromosomally (specification, page 28, lines 9-11). Thus, the arguments regarding "unpredictability due to site of insertion and copy number inserted" are irrelevant.

b) The Office argues that the claimed invention broadly encompasses any transgenic animal, including invertebrates. In response, and without acquiescing to the propriety of the rejection, Applicants have amended the claims to include the phrase "non-human vertebrate." Applicants reserve the right to pursue claims directed to the deleted subject matter in one or more continuing and/or divisional applications. Thus, the rejection is believed to be moot in view of the amendments to the claims.

c) The Office argues the claimed invention broadly encompasses any transgenic animal comprising any promoter. However, claims 1-3 have been amended and now claim a transgenic "non-human vertebrate" animal. Thus, the rejection is mooted in part, because the claims are no longer directed to "any transgenic animal." Further, claims 1-3 are believed to be free of the rejection since claims 1-3 require a transgenic non-human vertebrate animal comprising a transgene operably linked to a nucleotide sequence and do not claim any level of expression in any particular tissue.

The Office argues that "...while the specification enables an artisan to use a ubiquitous promoter and a bone-specific promoter, the specification does not teach an artisan how to use any promoter such as a skin- specific promoter or a neural-specific promoter such that expression of SEQ ID NO. 2 or SEQ ID NO. 1 results in transgenic animals that have a bone phenotype." (Office Action, page 15, lines 11-15). The foregoing arguments are presumably directed to claims 4-13, claiming modulation of bone mass in more than one parameter set forth in the claim since claims 1-3 do not claim a phenotype. Applicants disagree.

Regarding claims 4-13, one of skill using the methods and guidance disclosed in the specification would be able to determine whether a specific promoter did or did not direct protein expression, such that bone mass was modulated in more than one parameter as is claimed in claim 4. Contrary to the Office's arguments, the specification provides guidance as to how an artisan would make (*i.e.*, identify and then use) transgenic animals comprising a skin-specific or neural-specific promoter. The specification discloses identification of transgenic animals carrying the promoter-transgene, for example, by Southern and/or Northern blotting. One of skill could thus identify a transgenic animal carrying the desired promoter-transgene. The specification discloses methods for identifying changes in any of the claimed parameters. *See*, for example, pages 33, lines 15-28, showing methods of assessing bone modulation by measuring parameters such as bone mineral density and bone mineral content (measured by pDXA X-ray methods); bone size, bone thickness or volume (measured by X-ray); bone formation rates (measured by, for example, calcium labeling); and, total, trabecular and mid-shaft density (measured by pQCT and μCT methods). Presence of a particular promoter-nucleotide construct can be detected via Southern blotting and other techniques such as hybridization (disclosed, for example on page 41, lines 10-22 and page 147, line 6, through page 167, line 18; and, elsewhere throughout the specification). A transgenic animal comprising a particular promoter-transgene combination, where the promoter did not direct protein expression, would be identified by failure to detect expression of the protein, or fragment thereof, encoded by the linked nucleotide sequence.

Thus, undue experimentation is not required to practice the invention as claimed. The Office is reminded that even where "some" experimentation may be required, some experimentation does not rise to the level of "undue experimentation" where the methods for practicing the invention as claimed are disclosed in the specification.

The Office argues it would be undue experimentation for an artisan to practice the claimed invention without guidance as to how to assay the "biological effects" of HBM or LRP5 in the skin or nervous system. Contrary to the arguments, the biological effects of HBM or LRP5 in the skin or nervous system can be assayed using the chemical/biochemical/physical methods disclosed in the specification as discussed above (such as for example, protein expression and Northern blotting) as well as analysis of phenotype (page 167, lines 15-18).

d) The Office argues that the claimed invention broadly encompasses a transgenic animal comprising a transgene comprising SEQ ID NO: 2 or SEQ ID NO. 4 and that at the time of filing, the art teaches (citing to Hammer *et al.*) that an artisan cannot predict whether expression of a heterologous protein will result in a transgenic animal exhibiting a predictable phenotype. The Office further argues that the specification does not teach how to reliably make other transgenic animals, other than mice, that express SEQ ID NO: 2 or SEQ ID NO: 1 and exhibit a bone phenotype.

Applicants disagree. The claims do not claim any degree of predictability in making the claimed transgenic animals and none is required. As discussed above, whether a transgenic animal does or does not express a heterologous protein is easily determined by one of skill using the methods disclosed and guidance provided herein. Further, making transgenic animals from other species is well known in the art (*see*, for example, U.S.P.N. 6,872,869, filed Oct. 4, 2001, disclosing transgenic silkworms; U.S.P.N. 6,730,822, filed Oct. 16, 1998, disclosing transgenic chickens; U.S.P.N. 6,759,568, filed June 29, 2001, disclosing transgenic fish; U.S.P.N. 6,528,699, filed February 24, 1998, disclosing transgenic sheep, mice, pigs, cows, rabbits and goats; U.S.P.N. 6,372,956, filed Dec. 23, 1999, disclosing transgenic fish; and, U.S.P.N. 6,734,338, filed May 13, 1999, disclosing transgenic non-human primate, farm mammals and marine mammals), as are methods for assessing the nature of bone homeostasis. Bone density in all species accomodates to its customary loading conditions (*see*, specification page 178, lines 16-17) and methods for studying bone density are known in the art.

e) The Office argues the claimed invention encompasses a nucleic acid sequence "comprising at least 15 contiguous nucleotides of SEQ ID NO. 2 including at least the thymine at position 582 of SEQ ID NO. 2" (*see,* claim chart 1). According to the Office, Claim 1 allegedly encompasses any nucleic acid, including at least the thymine at position 582, read in any frame, which means that the peptides produced would encompass a peptide encoding part of HBM, and 2 other peptides which may not have any biological activity, and/or which may have biological activity, but nothing in the art or the specification teaches how to detect such activity. The Office alleges the claims encompass other embodiments which neither the specification nor the art teach how to use in transgenic mice comprising such embodiments.

Applicants traverse. The rejection is irrelevant, because the claims are not directed to transgenic animals expressing, or detection of, other peptides which may or may not have biological activity. As discussed above, whether the transgenic animal expresses a protein from a nucleotide sequence comprising at least 15 contiguous nucleotides of SEQ ID NO: 2 is readily determinable using the methods disclosed in the specification.

Further, Applicants note that claims 4-13 require the transgenic non-human vertebrate animal express a phenotype. Any transgenic animal, which lacks the phenotype, does not fall within the scope of the claim. Claims 4-13 exclude a transgenic animal which carries the sequence of 15 contiguous nucleotides but does not express the phenotype. Transgenic animals which do or do not have the phenotype are easily determined using the methods disclosed and guidance provide in the specification as discussed above. The Office is reminded some inoperative embodiments are allowed within the scope of the claims.

f) The Office argues the claimed invention encompasses a sequence comprising at least 15 contiguous nucleotides of SEQ ID No. 2 (Claim 1) or SEQ ID No. 1 (claim 4), which encompasses polynucleotides used as antisense. According to the Office, at the time of filing, the specification did not teach an artisan how to predictably obtain any 15-mer or longer polynucleotide and know that it would behave as antisense (sic: activity).

In reply, no claim recites a method for "predictably obtaining polynucleotides having antisense activity." Therefore, the rejection is erroneous. It is noted however, that the specification discloses antisense probes on page 97, lines 2-15; synthesis of antisense probes on page 97, line 16 through page 98, line 3; whether a candidate antisense probe has activity on page 98, lines 20-25 and particularly on pages 101, line 15 through page 106, line 7; discussing making and using antisense probes. Thus, contrary to the arguments of the Office, the specification provides support for making and using antisense probes.

g) The Office asserts (according to Merriam-Webster's online dictionary) "transgenic" means, "having chromosomes into which one or more heterologous genes have been incorporated either artificially or naturally" and that the word "transgenic" raises two issues with regards to claims 12 and 13. The Office argues that:

> "First, the transgenic animals in claim 1 encompass animals that are not fertile (*see,* claims 12 and 13), this means that there

> are some transgenic animals that cannot be continued as a line. This means that some transgenic animals comprising a certain genotype and phenotype are gone once the animal has died..... Second, the transgenic animals in claim 1 encompass animals that do not pass the transgene on to its offspring (*see* claims 12 and 13). In light of the fact that "transgenic" means that the heterologous gene had been incorporated into the chromosome and that some of the transgenic animals in claims 12 and 13 are not passing on the transgene to its offspring suggests a contradiction in terms and suggests that the transgenic animals are not really transgenic."

Office Action, pages 18-19.

In reply, the invention provides for a transgenic animal produced from the transgenic animals above or their offspring (page 13, lines 5-6). Not every transgenic animal produced has to be fertile. Claims 1, 3, and 4 do not require the transgenic to be fertile, which is different than in claims 12 and 13, which do. This event is considered in the specification (page 13, lines 5-6). A transgenic animal expressing a human HBM protein can be fertile and pass the human HBM gene to its offspring while non-fertile animals may still be used to study bone homeostasis.

In response to the Office concerns regarding the term "transgenic," the Office is directed to the discussion of the term "transgenic" in the instant specification. The specification discloses (page 28, lines 5-11):

> "A "transgenic animal" is an animal containing one or more cells bearing genetic information received, directly or indirectly, by deliberate genetic manipulation or by inheritance from a manipulated progenitor at a subcellular level, such as by microinjection or infection with a recombinant viral vector (*e.g.*, adenovirus, retrovirus, herpes virus, adeno-associated virus, lentivirus). **This introduced DNA molecule may be integrated within a chromosome, or it may be extra-chromosomally replicating DNA."** (emphasis added)

Thus, the meaning of the term "transgenic" as used by the Office is not entirely correct. The Office is reminded that an applicant is entitled to be his or her own lexicographer and may rebut the presumption that claim terms are to be given their ordinary and customary meaning by clearly setting forth a definition of the term that is different from its ordinary and customary meaning(s). *See, In re Paulsen*, 30 F.3d 1475, 1480, 31 U.S.P.Q.2d 1671, 1674 (Fed. Cir. 1994) (inventor may define specific terms used to describe invention, but must do so "with reasonable clarity, deliberateness, and precision" and, if done, must "'set out his uncommon definition in some manner within the patent disclosure' so as to give one of ordinary skill in the art notice of the change" in meaning) (quoting *Intellicall, Inc. v. Phonometrics, Inc.*, 952 F.2d 1384, 1387-88, 21 U.P.Q.2.d 1383, 1386 (Fed. Cir. 1992)). Where an explicit definition is provided by the applicant for a term, that definition will control interpretation of the term as it is used in the claim. *Toro Co. v. White Consolidated Industries Inc.*, 199 F.3d 1295, 1301, 53 U.S.P.Q.2d 1065, 1069 (Fed. Cir. 1999) (meaning of words used in a claim is not construed in a "lexicographic vacuum, but in the context of the specification and drawings"). Any special meaning assigned to a term "must be sufficiently clear in the specification that any departure from common usage would be so understood by a person of experience in the field of the invention." *Multiform Desiccants Inc. v. Medzam Ltd.*, 133 F.3d 1473, 1477, 45 USPQ2d 1429, 1432 (Fed. Cir. 1998). *See* also *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 U.S.P.Q.2d 1029, 1033 (Fed. Cir. 1999) and M.P.E.P. § 2173.05(a). As the rejection is based on an incorrect meaning as used by the Office, the rejection is erroneous and should be withdrawn.

h) The Office argues the transgenic animals of claim 4 comprising a transgene construct comprising a nucleic acid sequence encoding LRP5 operably linked to a promoter exhibit a phenotype wherein bone mass is modulated. The Office argues while the specification teaches how to use transgenic animals wherein bone mass increases, the specification does not teach how to use transgenic animals where bone mass decreases, and concludes that it would be undue experimentation for an artisan to use a transgenic animal wherein bone mass decreases because nothing in the specification teaches an artisan the relationship between overexpression of LRP5 and bone loss.

In reply, claim 4 (and dependent claim 13) has been amended to now claim SEQ ID NO: 2 (the HBM sequence). Thus, the amendments to claim 4 are believed to overcome the rejection, directed to a nucleic acid sequence encoding HBM.

In view of the amendments to the claims and arguments presented above, the rejections under 35 U.S.C. § 112, first paragraph, are believed to be overcome. Reconsideration and withdrawal of the rejection is respectfully requested.

4. Rejection under 35 U.S.C. § 112, first paragraph (written description)

Claims 1-13 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The rejection is respectfully traversed.

A. The Office asserts only the full length SEQ ID NO. 2 and SEQ ID NO. 1 meet the written description provision of 35 U.S.C. § 112, first paragraph and that Applicants were not in possession of the claimed genus of transgenic animals comprising at least 15 contiguous nucleotides of SEQ ID NO:2 including at least the thymine at position 582. The Office asserts the written description requirement for a claimed genus is satisfied by sufficient description of a representative number of species by actual reduction to practice and by disclosure of relevant identifying characteristics, *i.e.*, structure or other physical and/or chemical properties by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show applicant were in possession of the claimed genus. According to the Office, in the instant case, while the Applicants have demonstrated a transgenic animal comprising SEQ ID NO. 2 or SEQ ID NO. 1, Applicants have not taught the function of every 15-mer oligonucleotide up through the full length sequence of SEQ ID NO. 2, wherein any peptide encoded by any oligonucleotide of SEQ ID NO. 2 comprising at least the thymine at position 582 of SEQ ID NO. 2 has any activity. Lastly, the Office argues the specification has not taught that all 15-mer and longer nucleotides behave as an antisense construct.

Applicants disagree with the position of the Office. There are three independent claims currently under examination, claims 1, 2 and 4. Claim 1 is directed, *inter alia*, to a transgenic non-human vertebrate animal comprising a promoter region operably linked to a sequence comprising at least 15 contiguous nucleotides of SEQ ID NO: 2 including at least the thymine at position 582 of SEQ ID NO: 2. Claim 1 thus requires an animal, a promoter and a nucleotide sequence comprising a nucleotide sequence of at least 15 contiguous nucleotides of SEQ ID NO: 2 which includes a thymine at position 582. The claim does not claim that all 15-mer and longer nucleotides behave as an antisense construct. Therefore, that basis for rejection is erroneous. As stated above, to the extent that the nucleotide sequence encodes non-operative proteins, the claims are allowed to include some inoperative embodiments.

Claim 2 is directed to, *inter alia*, an animal comprising a sequence encoding SEQ ID NO: 4. Claim 2 does not include the text "at least 15 contiguous nucleotides," does not suffer from the alleged deficiencies cited by the Examiner, and is therefore erroneously rejected for the reasons stated therein.

Claim 4, while comprising the text "at least 15 contiguous nucleotide," also requires that any transgenic animal falling within the scope of the claim also express a phenotype. Therefore, the nucleic acid sequence comprising the "at least 15 contiguous nucleotides" would also necessarily have to include sufficient sequence of the HBM gene, such that the protein expressed from the encoded sequence would result in the claimed phenotype. The Office is directed to the teachings in the specification, for example, at page 45, line 26 through page 46, line 15; discussing that the HBM peptides produced are considered to include peptides having conservative substitutions and other changes. In addition, the specification provides both the nucleotide sequence and amino acid sequence of the full length HBM protein. Thus, one of skill would easily be able to determine the sequence of a contiguous 15-mer which must include position 582.

The rejection is believed to be overcome in view of the amendments to the claims and arguments above. The rejections are not believed to be applicable to new claims 45 and 46. Reconsideration and withdrawal of the rejection of claims 1-13 is respectfully requested.

5. **Rejection of claims 1-13 under 35 U.S.C. § 103**

Claims 1-13 are rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Carulli *et al.*, U.S. Patent No. 6,770, 461, filed April 5, 2000, issued August 3, 2004 [Carulli], in view of Watson *et al.*, 1993, "The Introduction of Foreign Genes into Mice," Molecular Biology of Recombinant DNAs," 2nd Edition, pp. 255-272 [Watson]. The rejection is respectfully traversed. Claims 1-13 have been amended. Claims 45 and 46 are newly added.

The Office argues Carulli teaches subjects that express the HBM gene, a mutant form of the Zmax1 gene, tend to have increased bone density and do not develop osteoporosis. The Office asserts Carulli does not teach a transgenic animal comprising a transgene construct comprising a nucleic acid sequence encoding Zmax or HBM operably linked to a bone specific promoter or a constitutive promoter, wherein the transgene construct is stably integrated into the host animal's genome. According to the Office, Watson allegedly cures the deficiency of Carulli. Watson is cited for teaching the generation of transgenic mice by pronuclear injection and that the technique can be used to introduce a transgene construct that can be stably integrated into a mouse's genome (page 256, first column, second paragraph, lines 1-23). The Office concludes it would have been *prima facie* obvious at the time the application was filed to make a transgenic mouse comprising a transgene construct comprising a nucleic acid sequence encoding Zmax1 or HBM operably linked to a constitutive promoter or a bone specific promoter, wherein the transgene construct was stably integrated into the genome in order to obtain a model system that can be used to study the pathways involved in osteoporosis. According to the Office, motivation to combine the references was provided by Carulli *et al.* for teaching the relationship between bone and HBM and Zmax1.

Contrary to Office arguments, Carulli does disclose transgenic mice and that the transgenic mice carry the HBM gene in the mouse homologue. *See*, column 88, line 58 through column 89, line 7. However, claims 1-13 are not rendered obvious by Carulli for reasons which follow. Claims 1 and 2 are newly amended herein to recite the term "bone" in the phrase "animal and/or human bone cells." Claims 45 and 46 are newly added.

Zmax1 is the wild-type of HBM and is also referred to as LRP5 (*see*, specification page 9, "Summary"]. Carulli discloses identification of the Zmax1 gene and the HBM variant (column 6, lines 16-28), hypothesizes gene treatment of normal individuals with the HBM variant or protein (column 6, lines 25-28), or fragments thereof, to ameliorate osteoporosis (column 6, lines 25-28). Carulli also discusses treatment of conditions of secondary osteoporosis involving, for example, bone remodeling, and methods for treating, diagnosis, preventing or screening for osteoporosis and transgenic animals carrying the HBM variant in the mouse homologue (column 88, line 58 through column 89, line 7). Carulli fails to disclose, however, a transgenic non-human vertebrate animal comprising a promoter region operably linked to a sequence, comprising at least 15 contiguous nucleotides of SEQ ID NO: 2 comprising at least the thymine at position 582, directing protein expression in bone cells. Watson, teaching the generation of transgenic mice by pronuclear injection, is silent on (1) the HBM gene, (2) a nucleotide sequence comprising at least 15 contiguous nucleotides of SEQ ID NO: 2 including at least the thymine at position 582 of SEQ ID NO: 2, and (3) a promoter directing expression in bone cells. Watson, having its own deficiencies, thus fails to cure the deficiencies of Carulli.

Carulli teaches the HBM variant and transgenic animals, but is silent on a transgenic animal having a nucleotide sequence comprising a promoter region that directs protein expression in bone cells. Watson teaches the production of transgenic animals but is silent on the HBM variant and portions thereof, and a nucleotide sequence comprising a promoter region that directs protein expression in bone cells. Thus, there is no motivation to combine the references since Watson generically teaches making transgenic animals comprising any gene. Watson fails to suggest production of transgenic mice comprising a nucleotide sequence comprising a promoter region that directs protein expression in bone cells because Watson fails to direct the skilled artisan to choose between the many possible choices of genes or promoters to obtain the now claimed animals. Thus, both the Carulli and Watson documents are silent on nucleotide sequences comprising promoter regions that direct protein expression in bone cells. New claim 45, dependent from claim 1, is free of the rejection since claim 1 is now believed to be free of the cited prior art.

Claims 4-13 are free of the rejection over Carulli and Watson since neither document discusses production of transgenic animals, wherein the bone mass is modulated relative to non-transgenic animals in more than one parameter selected from the group consisting of "bone density, bone strength, trabecular number, bone size and bone tissue connectivity."

As the Office is aware, "[i]n determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re Linter*, 458 F.2d 1013, 1016, 173 U.S.P.Q. 560, 562 (C.C.P.A. 1972). In view of the silence of Carulli and Watson on, *inter alia*, "a nucleotide sequence comprising promoter regions that direct protein expression in bone cells," the teachings of the documents are not sufficient for one of skill in the relevant art to make the proposed combination and arrive at the invention as claimed.

New claim 46 is free of the rejection, because it requires a bone specific promoter region that directs protein expression in animal and/or human cells. One of skill, reading Watson, does not find the suggestion to produce transgenic mice comprising a nucleotide sequence comprising a bone-specific promoter region that directs protein expression in cells as there is no guidance in Watson as to which of the many possible choices of genes or promoters would give the expected result. Carulli discloses a transgenic mouse carrying the HBM gene but does not specifically suggest a nucleic acid sequence comprising a bone specific promoter that directs protein expression in animal and/or human cells as discussed above. Thus, neither Carulli nor Watson, taken alone or in combination, renders obvious the invention of claim 46.

Thus, because the references, viewed alone or together, fail to suggest the claims, a rejection based on a *prima facie* case of obviousness is improper. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited. In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

If any fees are required or if a Notice of Appeal fee is required to maintain pendency, the Office is asked to charge Deposit Account No. 50-0573. The Office can credit any overpayments to the Account.

Respectfully submitted,
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Substitute for forms 1449A/PTO & 1449B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

ATTORNEY'S DKT NO. 032796-179	APPLICATION NO. 10/680,287
APPLICANT G. Roger Askew et al.	
FILING DATE October 8, 2003	GROUP ~~Unassigned~~ 1632

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U.S. PATENT DOCUMENTS

Examiner Initials	Document Number	Kind Code (if known)	Name of Patentee or Applicant of Cited Document	Issue/Publication Date (MM-DD-YYYY)
JH	5,691,153		Robert R. RECKER et al.	
↓	6,545,137	B1	Todd et al.	04-08-2003
↓	6,555,654	B1	Todd et al.	04-29-2003

FOREIGN PATENT DOCUMENTS

Examiner Initials	Document Number	Kind Code (if known)	Country	Date of Publication (MM-DD-YYYY)	Translation Yes	Translation No
JH	WO 99/47529		PCT	09-23-1999	X	
↓	WO 97/12903		PCT	04-10-1997	X	
↓	WO 99/09054		PCT	02-25-1999	X	
↓	WO 98/46743		PCT	10-22-1998		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Include name of author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.
JH	Annex Form PCT/ISA/206 Communication Relating to the Results of the Partial International Search attached to Invitation to Pay Additional Fees dated May 7, 2001 in PCT/US00/16951 filed on June 21, 2000
↓	A. ~~COURSEAUX et~~ al., *"Homo Sapiens Chromosome 11 Clone BAC67-M-5 MAP 11q13, *** Sequencing in Progress ***, 3 Ordered Pieces"*, Database EM_HTG, E.B.I., Hinxton, U.K., Accession Number: AC024123, March 2, 2000, XP002165276, Abstract
JH	D.L. KOLLER *et al.*, *"Linkage of a QTL Contributing to Normal Variation in Bone Mineral Density to Chromosome 11q12-13"*, J. Bone Miner. Res., Vol. 13, No. 12, pp. 1903-1908, December 1998, Blackwell Science, Inc., American Society for Bone and Mineral Research, USA
↓	Michael P. WHYTE, *"Searching for Gene Defects that Cause High Bone Mass"*, Am. J. Hum. Genet., Vol. 60; No. 6, pp. 1309-1311, June 1997, The American Society of Human Genetics, USA
↓	Marion TROMMSDORFF *et al.*, *"Interaction of Cytosolic Adaptor Proteins* with Neuronal Apolipoprotein E Receptors and the Amyloid Precursor Protein", J. Biol. Chem., Vol. 273, No. 50, pp. 33556-33560, December 1998, The American Society for Biochemistry and Molecular Biology, Inc., USA
	~~S. SCHNEIDER~~ *et al.*, *"Formation of Focal Adhesions by Osteoblasts Adhering to Different Substrata"*, Experimental Cell Research, Vol. 214, No. 1, pp. 264-269, September 1994, Academic Press, Inc., USA
JH	Frederick M. PAVALKO *et al.*, *"Fluid Shear-Induced Mechanical Signaling in MC3T3-E1 Osteoblasts Requires Cytoskeleton-Integrin Interactions"*, Am. J. Physiol., Vol. 275, No. 6 (Pt1), pp. C1591-1601, December 1998, The American Physiological Society, USA
↓	Mark L. Johnson *et al.*, *"Linkage of a Gene Causing High Bone Mass to Human Chromosome 11 (11q12-13)"*, Am. J. Hum. Genet., Vol. 60, No. 6, pp. 1326-1332, June 1997, The American Society of Human Genetics, USA
↓	Dong-Ho KIM *et al.*, *"A New Low Density Lipoprotein Receptor Related Protein, LRP5, is Expressed in Hepatocytes and Adrenal Cortex, and Recognizes Apolipoprotein E"*, J. Biochem., Vol. 124, No. 6, pp. 1072-1076, December 1998, The Japanese Biochemical Society, JAPAN

Examiner Signature	Joan	Date Considered	5/19/05

EXAMINER: Initial if reference considered, whether or not citation is in conformance with M.P.E.P. § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.